CHAPTER 7
MECHANISM OF HYDROTROPIC PHENOMENON

7.1 INTRODUCTION

The unprecedent solubilizing effect of hydrotropes above MHC evoked the academic curiosity to investigate the possible mechanism of hydrotropic phenomenon.

7.2 REVIEW OF PREVIOUS MECHANISMS

Over the years, attempts have been made to suggest the mechanism of hydrotropy. In the earlier attempts, salting-in effect and co-solvency were considered by Mckee (1946) and Winsor (1948). Licht and Wiener (1950), Deno and Spink (1963) have attributed the hydrotopic solubilization as salt effect. Neuberg (1930) suggested that the hydrotropic solubilization is due to the formation of a compound between the hydrotrope and the solute. Bockris et al (1957) considered electrostatic forces in addition to the dispersion effect for this technique. Korenmann (1974) suggested that the solubilization may be due to the formation of weak complexes between the hydrophobic compound and the hydrotrope. Earlier, Rath (1965) visualized the possibility of intermolecular interaction between hydrotrope and the solute.

The mechanisms suggested by these authors have been based purely on theoretical knowledge and not supported by any experimentation. However Badwan et al (1982) and Balasubramanian et al (1989) have suggested certain mechanism based on their experimental findings.
The theme of self association of hydrotrope molecules was proposed by Badwan et al (1982) as the basis for their mechanism for hydrotropy. They carried out a study on the solubility of benzodiazepine derivatives using hydrotrope solutions. The effect of hydrotrope to bring significant solubilization of benzodiazepine derivatives was observed by them only from a certain concentration of hydrotrope in the aqueous phase. As per their view, this particular concentration was required for the formation of a complex by the association of hydrotrope molecules. However, for more clarification, they suggested further studies on the changes in the solution properties of hydrotropes with increase in hydrotrope concentration in the aqueous phase.

Hydrotropes even claim to form intramolecular stack like association with the solute molecules as reported by Gaikar et al (1986). Balasubramanian et al (1989) have termed the concentration of hydrotrope in the aqueous phase from which the solubilization of the solute actually takes place as Minimum Hydrotrope Concentration (MHC) which was earlier pointed out by Badwan et al (1982). While working on solutes such as fluorescein diacetate, perylene and ethyl p-nitrobenzoate in aqueous solutions of hydrotropes namely sodium xylene sulfonate, sodium cumene sulfonate, they found that a minimum concentration of hydrotrope was necessary in the aqueous phase to initiate the solubilization of the solute.

They attributed the increase in solubilizing effect to the formation of self association of hydrotrope molecules among themselves to form organized aggregates, which attract the solute molecules inside the aqueous phase. They also pointed out the possibility of such aggregates having some properties similar to that of surfactants.
7.3 MECHANISM OF HYDROTROPIC RESPONSE

Hydrotropes in general fail to generate spontaneous self assembly towards equilibrium mesoscale structures in aqueous solutions due to their amphiphilic structured molecules. The solubility enhancement of hydrophobic compounds in aqueous solutions were initiated by the formation of dynamic, non-covalent assemblies which intend to create microscopic regions of lowered polarity.

The response of hydrotropes in aqueous solution is phenomenol above a significant concentration due to the self aggregating capability. From the analysis of experimental data, it can be observed that there is a possibility of hydrotrope molecules forming self association forming micelle like aggregates above MHC. However hydrotropes being classified in a broad manner, there is no unique mechanism exhibiting the aggregation behavior of hydrotropes. Hydrotropic molecules associate as a pack of two dimensional sandwich manner consisting of alternating hydrophobic or hydrophilic regions, as reported by Srinivas et al. The solubilizates (organic solutes considered in the present investigation) were anticipated to induce into the hydrophobic regions in an intermeshing manner. Hence it can be inferred that, these open layer assemblies tend to be supportive in enhancing the solubility of the hydrophobic organic solutes.

The mechanism of hydrotropic phenomenon is unclear still, but possibilities can be enumerated regarding hydrotropic response.

(a) Possibility of interaction between the hydrotrope molecule and the solubilizate molecule, by the formation of complex intending to higher aqueous solubility.
(b) Possibility of change in the structure around the solubilizate, thus serving as structure makers or structure breakers.

(c) Possibility of forming spherical aggregates, where the hydrotrope molecules tend to surround the solubilizate molecules.

7.4 SHORTCOMINGS OF PREVIOUS MECHANISMS

Even though the case of MHC and association formation has been pointed out by Badwan et al (1982) and Balasubramanian et al (1989), no clear-cut mechanism has been suggested by them for the following characteristics of hydrotropes exhibited at various stages of the present study.

1. Reason for the inaction of hydrotropes below MHC values.

2. Explanation for the increased solubilization of the solute with increase in hydrotrope concentration.

3. Saturation of the solubilizing effect of hydrotrope beyond a particular concentration, $C_{\text{max}}$.

4. The property, by which aggregate of hydrotrope molecules at MHC was able to initiate the solubilization of the solute molecules into the aqueous phase.

5. The ability of such aggregate of hydrotrope molecules to retain the solubilized solute well within the aqueous phase, inspite of the immiscible nature due to the difference in the polarity of the solute and aqueous phase.
In this study, an attempt has been made to propose a mechanism of hydrotropic phenomenon from a different angle and to explain the various characteristics exhibited by hydrotropes used in this work.

7.5 PROPOSED MECHANISM

The advent of the principle of MHC for each hydrotrope by Badwan et al (1982) and Balasubramanian et al. (1989) has opened up more avenues for the experimental studies on various solutes in different hydrotrope solutions. Previous workers have suggested various theories like salting-in-effect, complex formation, cosolvency, association of hydrotrope molecules, intermolecular interactions etc., for the contribution of hydrotropic effect towards many organic and inorganic solutes. However no consistent idea on the mechanism of hydrotropy has been arrived until now.

In the present work, a comprehensive study on the effect of various hydrotropes on the solubility and mass transfer coefficient of a series of organic compounds has been carried out. It has been ascertained that in the case of organic solute also, a certain minimum concentration of hydrotrope in the aqueous phase similar to the one proposed by Badwan et al (1982) and Balasubamanian et al (1989) was found essential to observe a significant increase in the solubility.

Therefore, it has become quite clear that whatever be the type of hydrotrope that is being used in the aqueous phase, a minimum concentration of hydrotrope is necessary to initiate the solubilization activity of a hydrotrope.

From the analysis of the experimental data, it has been observed that the solubility of the solute increases with increase in hydrotrope concentration and the solubilizing effect of hydrotropes is not a linear
function with the hydrotrope concentration. It was also seen that MHC values of various hydrotropes used in this study range between 0.20 to 0.60 mol.L\(^{-1}\) with respect to different organic solutes selected. In other words, for the same aqueous phase concentration, different number of hydrotrope molecules is required to form aggregates at MHC values. This range of critical MHC values may be due to the difference in the hydrophilic nature of the hydrotropes in the aqueous phase. Such a significant concentration of hydrotrope required in the aqueous phase suggests the formation of a certain complex arrangement of the hydrotrope molecules in the aqueous phase.

In order to explain the theory of complex arrangement, a study on the solution properties like viscosity, specific gravity, surface tension, specific conductance and refractive index of hydrotropes for a range hydrotrope concentrations (0.00-2.00 mol.L\(^{-1}\)) has been carried out. Figures 7.1 to 7.5 represents the plot of viscosity, specific gravity, surface tension, specific conductance and refractive index of hydrotrope solution vs hydrotrope concentration for different hydrotropes studied.

From the Figures it can be seen that the trend in the change of solution properties with hydrotrope concentrations is a linear one up to the critical concentration corresponding to MHC values, after which a distinct deviation from linearity has been observed.

The positive deviation in the viscosity plot (Figure 7.1) indicates that aggregate formation is associated with an increase in viscosity of hydrotrope concentration, which is in agreement with the self-association of phenolic compounds (Thomas 1960).

The plot of specific gravity versus hydrotrope concentration showed a negative deviation (Figure 7.2) that indicates an increase in partial molal volume upon aggregation, and this increase in volume may be due to
expansion of the hydrocarbon portion of the molecule or its partial removal from the high compressive force of water.

The surface tension plot (Figure 7.3) showed a moderate decrease in surface tension on increasing the hydrotrope concentration as hydrotropes are not surface active agents (Saleh, et al 1983; Saleh and Daabis 1974). The deviation from linearity in specific conductance plot (Figure 7.4) is strongly indicative of molecular aggregation (Mukerjee 1967).

The plot of refractive index versus hydrotrope concentration (Figure 7.5) showed negative deviation. It was revealed from different studies that at lower hydrotrope concentration, there were weak ionic interactions while at higher hydrotrope concentration, the molecular aggregation seems to be the possible mechanism of hydrotropic solubilization (Saleh 1983, Saleh and El-Khordagui 1985, Neuberg 1916, Winsor 1950, Yalkowsky 1999, Sanghavi 2002).

Therefore, it can be concluded that the significant solubilizing effect of hydrotropes above MHC may be due to the fact that hydrotrope molecules probably associate into organized aggregates at this critical concentration. It may be suggested that the deviation from linearity of solution properties observed is an indication of aggregate formation, when the concentration surpasses this critical value. In other words, this deviation may be considered to be the characteristic of hydrotropic solubilization.

Hence, the formation of aggregates of hydrotrope molecules with the attainment of MHC can be taken as a pre-requisite to display this phenomenon.

It may be further assumed that the formation of such aggregates creates a new surface environment with different solution properties like
viscosity, specific gravity, surface tension, specific conductance and refractive index. This has been indicated in the study on solution properties also. Possibly the change in surface tension and hence polarity at MHC enable the solute molecules to clinch to MHC aggregates to be retained in the aqueous phase. Such critical surface-active properties of hydrotrope aggregates seem to initiate the solubilization effect of hydrotropes.

The increase in the solubilizing effect with increase in hydrotrope concentration may be due to the more number of such aggregates available for interaction with solute molecules at the existing conditions of the aqueous phase.

Further formation of hydrotrope aggregates with increased hydrotrope concentration in the aqueous phase depends on the availability of water molecules also, since by hydration theory, every water molecule forms associated structure among themselves and influences other polar substances in it to form similar association of molecules.

![Figure 7.1 Plot of viscosity versus hydrotrope concentration for different hydrotropes](image-url)
Figure 7.2  Plot of specific gravity versus hydrotrope concentration for different hydrotropes

Figure 7.3  Plot of surface tension versus hydrotrope concentration for different hydrotropes
Figure 7.4  Plot of specific conductance versus hydrotrope concentration for different hydrotropes

Figure 7.5  Plot of refractive index versus hydrotrope concentration for different hydrotropes
This complex arrangement may be visualized as the formation of a stack of hydrotrope aggregates with that of solute molecules. It can also be visualized that such a staking arrangement of solute molecules are sandwiched between hydrotrope aggregates one upon the other. This stacking can be assumed as a sheet of solute molecules held captive between hydrotrope aggregates. However such a stacking arrangement need not have any geometric restrictions, that is to say that no regular pattern of stacking can be stressed upon.

Further increase in the solubilizing effect of hydrotrope beyond maximum hydrotrope concentration $C_{\text{max}}$ has been hampered because hydrotrope molecules are handicapped with the non-availability of water molecules to form aggregates. This explains the saturation of the solubilizing effect of hydrotropes beyond $C_{\text{max}}$, which can be observed from the experimental data.

It appears that the solute molecules after finding their way through the interface of hydrotrope aggregates are held hidden in the hydrotropic stack.

Though, by nature, the solute and aqueous layers are immiscible because of difference in polarity, the hydrotrope aggregates are able to hold them within the possible hydrotropic stack, because of different solution properties acquired by them. Such a situation is not visible to the naked eye probably due to the negligible difference in the surface tension and other allied properties of the hydrotropic stack which contains the hidden solute and aqueous phase.
However, this arrangement seems to be a purely temporary one, because the solute particles contained within the hydrotrope stack can be brought out by simple dilution with distilled water, which alters the solution properties of hydrotrope stack. This causes the dissociation of hydrotrope molecules and the properties of hydrotrope solutions with decrease in hydrotrope concentration approach to that of water, similar to the situation below MHC. This phenomenon was observed experimentally by release of the dissolved solute from hydrotrope solutions at any concentration between MHC and $C_{\text{max}}$ by simple addition with distilled water and hence possible re-use of hydrotrope solutions.

In general, the sort of host-guest interaction between the hydrotrope aggregates and solute molecules seems to contribute significantly to the overall stability of the solute-hydrotrope system.

### 7.6 MICROSCOPIC STUDIES

The Scanning Electron Microscope (SEM) uses a beam of high energy electrons to generate a variety of signals at the surface of solid samples. The electron-sample interactions reveal information about the sample’s surface topography. Signals produced by SEM result from interactions of the electron beam with atoms at or near the surface of the sample. The relative narrower electron beam produced by SEM yields a characteristic three-dimensional appearance useful for investigating the surface of objects. The SEM is also capable of determining chemical composition, crystalline structure and crystal orientations.

Experimental data on solubility and mass transfer coefficient enhancement of various solute-hydrotrope systems were analysed and
discussed in previous chapters. In this section, Scanning Electron Microscope (SEM) images of L-aspartic acid i.e., the only solute in solid phase are presented. In addition an enhancement factor (\( \Phi_e \)) of 13.52 has been observed for L-aspartic acid-nicotinamide system at a temperature of 333 K.

Figure 7.6 shows SEM image of pure L-aspartic acid at 200 µm, 100 µm and 20 µm. A close observation of the image indicates brick tile shaped structures, representing the crystallinity of L-aspartic acid. Figure 7.7 shows SEM image of solubilized L-aspartic acid with nicotinamide hydrotrope at 50 µm, 20 µm and 10 µm. A compact cluster like formation was indicated at 50 µm and 20 µm L-aspartic acid along with nicotinamide reveals an image of compact cluster like formation as observed at 50 µm, whereas at 20 µm, clearly representing that L-aspartic acid is being agglomerated with nicotinamide following positive aggregation phenomenon.
Figure 7.6 SEM image of Pure L-Aspartic acid at various micrometres (µm)
Figure 7.7  SEM image of solubilized L-Aspartic acid with nicotinamide at various micrometres (µm)